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EXAMINER

ARCHIE, NINA

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

ADVISORY ACTION

1. The amendment filed on 1/12/2009, in reply to the final rejection has been considered and will be entered but is not deemed to place the application in condition for allowance. Amendments and applicant's remarks have been entered. Claims 28-34 and 36 are currently pending and under examination. Claim 35 is cancelled. Claims 30 and 34 are withdrawn from consideration.

Claim Rejections Maintained Double Patenting

2. The rejection of claims 28 and 36 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 101, 107-109, 120-122, 124 of copending Application No. 10/314,578 are maintained for the reasons set forth in the previous office action.

Applicant arguments:

Claims 28 and 36 have been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 101, 107-109, 120-122 and 124 of co-pending Application No. 10/314,578. Applicant's arguments have been dismissed because according to the Examiner US 7271156 shares a common inventor with the present application. Applicant disagrees.

As far as Applicant is aware, neither the case law nor the MPEP states that two patent applications which are not commonly owned (identical ownership) and which don't have identical inventorship are subject to obviousness type double patenting. Application of double patenting in a circumstance when the patents are not commonly owned and do not have identical inventorship and the claims under rejection have the earliest effective priority date would be contrary to the public policy reason for double patenting. The public policy behind the double patenting doctrine is to allow the public to freely use a patent upon its expiration and to prevent an entity from obtaining multiple patents on one

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invention including obvious variations. "The basic concept of double patenting is that the same invention cannot be patented more than once, which, if it happened, would result in a second patent which would expire some time after the original patent and extend the protection time wise." *General Foods Corp. v. Studiengesellschaft Kohle M'bH*, (972 F.2d 1272, 1279, 23 USPQ2d 1839, 1844 (Fed. Cir.. 1992)). (See also *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993) and MPEP 804B). The judicially created doctrine of obviousness type double patenting was originally implemented to prevent issuance of two patents that otherwise did not qualify as prior art against one another. The instant application is prior art under 35 USC 102(e) against US 7271156. US 7271156 which has an earliest effective priority date of September 25, 1999 is not prior art under any other section of the statute against the instant applicants or any other party that filed a patent application prior to 1999. Further, issuance of the instant patent application would not extend the patent protection beyond a point by which the public would otherwise be free to use the technology. To apply a double patenting rejection in the instant circumstance would extend beyond the purpose of the nonstatutory obviousness-type double patenting. Thus, double patenting is not appropriate in the instant circumstance.

Examiner's Response to Applicant's Arguments:

Examiner disagrees with Applicant's assertion because the inventions do not have common ownership, this rejection would maintain as an obviousness-double-patenting rejection (see MPEP 804 Chart IIB). Although Applicants, stated that US 10/314,578 is a later filed application, which has now issued as US 7271156 does not share common ownership. However, US 10/314,578 is a later filed application, which has issued as US 7271156 and does share a common inventor with the present application therefore the rejection is maintained.

Claim Rejections Maintained - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

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(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Rejections Maintained

2. Claims 28-34 and 36 are rejected under 35 U.S.C. 103(a) is maintained for the reasons set for in the previous office action on 9/12/2008.

3. The rejection of claims 28-29, 31-33, and 36 under 35 U.S.C. 103(a) as being unpatentable over Kuramoto et al 1992 Jpn J. Cancer Res Vol. 83 pgs. 1128-1131 in view of Goodchild et al 1990 The American Chemical Society, Vol. 1, No. 3 pgs. 165-182, Hutcherson et al US Patent 5,723,335 March 3, 1998 (filed March 25, 1994), and Cheng et al US Patent No. 5,646,126 July 8, 1997 (filed February 28, 1994) are maintained for the reason set forth in the previous office action.

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4. The rejection of claims 28-29, 31-33, and 36 under 35 U.S.C. 103(a) as being unpatentable over Kataoka et al 1992 Jpn. J. Cancer Res. Vol. 83 pgs. 244-247 in view of Goodchild et al 1990 The American Chemical Society, Vol. 1, No. 3 pgs. 165-182, Hutcherson et al US Patent 5,723,335 March 3, 1998 (filed March 25, 1994), and Cheng et al US Patent No. 5,646,126 July 8, 1997 (filed February 28, 1994)) are maintained for the reason set forth in the previous office action.

Applicant arguments:

The skilled artisan at the time of the invention would not have combined the teachings of Kuramoto et al or Kataoka et al with Goodchild or Hutcherson to produce the ODN of Kuramoto et al or Kataoka et al having phosphorothioate internucleotide linkages for reasons provided in more detail below. It is only in hindsight, using Applicant's disclosure would the skilled artisan have been motivated to make such a combination. The skilled artisan at the time of the invention would not have combined the teachings of Kuramoto et al or Kataoka et al with Goodchild to produce a phosphorothioate modified ODN because of the unpredictability of phosphorothioate backbone modifications. At the time of the invention it was unknown whether phosphorothioate backbones should be used with immunostimulatory oligonucleotides. It was not clear how a change in backbone would affect the properties of phosphodiester based immunostimulatory oligonucleotides. Applicant previously cited several papers as evidence that it was unpredictable.

In response to Applicant's arguments the Examiner cited Agrawal and Hutcherson as support that the skilled artisan would have used phosphorothioate linkages in immunostimulatory ODN. It is stated in the Office Action (pages 9-10) that Agrawal teaches that phosphorothioate backbones "should be used with immunostimulatory oligonucleotides". Applicant is not aware of such a teaching in Agrawal et al. Agrawal et al (US Patent No. 5194428) describes antisense ODN for treating influenza virus infection. In particular it is taught that the antisense ODN "have antiviral activity against influenza virus as a result of their ability to hybridize to a selected region of influenza virus RNA and inhibit its ability to serve as a template for synthesis of encoded

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products". (Abstract). Antisense is a different mechanism of action than immune stimulation. Agrawal does not provide a teaching to the skilled artisan that phosphorothioate backbones should be added to immunostimulatory ODN.

It is further stated in the Office Action that Hutcherson et al teach that phosphorothioate ODN analogs enhance immune stimulation. However, the skilled artisan would not have modified the ODN of Kuramoto et al or Kataoka et al to add phosphorothioate linkages based on the teachings of Hutcherson because the teachings of the two references are inconsistent and further in view of the known unpredictability of the phosphorothioates in the art, as discussed below. Kuramoto et al and Kataoka et al teach that the immunostimulatory DNA is representative of immunostimulatory bacterial DNA.

Bacterial DNA is not phosphorothioate modified. Kuramoto et al and Kataoka et al further teach that the immunostimulatory activity of the ODN is due to the hexameric palindrome within the sequence. Hutcherson describes generally that phosphorothioate ODN analogs can provoke an immune stimulatory response. However, Hutcherson does not provide any teaching regarding inclusion of a palindrome. In fact, Hutcherson et al. teaches that it is the phosphorothioate internucleotide linkage that has immunostimulatory activity. The skilled artisan attempting to create a synthetic version of bacterial DNA that was immunostimulatory would not have been motivated to phosphorothioate modify it because of the teachings of Hutcherson. Hutcherson is describing molecules that are distinct from Kuramoto et al and Kataoka et al in that they are phosphorothioate modified and are sequence independent.

The skilled artisan would have expected that the molecules of Kuramoto et al/Kataoka et al and Hutcherson were operating through different mechanisms. Without knowledge of the mechanisms through which these nucleic acids achieved immune stimulation, it would have been unpredictable to one of ordinary skill in the art whether a phosphate backbone modification would totally destroy the immunostimulatory capability of the Kataoka or Kuramoto nucleic acids. In the absence of the work of the instant invention it would not have been known at the time of the invention whether a phosphorothioate bond or phosphorodithioate bond would substantially change the shape of the oligonucleotide so as to totally destroy immunostimulatory ability.

Further, Applicants presented evidence of the unpredictability of phosphorothioate linkages. As none of that evidence has been addressed, Applicant reiterates those arguments. A 1993 Science paper by Stein et al (Science v. 261 p. 1004 1993) shows that phosphorothioate modifications can have unpredictable effects on an oligonucleotide. In fact, phosphorothioate can unpredictably redirect oligonucleotide activity to create biological activity against targets where there previously was none. Phosphorothioate modifications have many more biological effects than simply reducing oligonucleotide degradation in vivo. As detailed in Stein et al those effects were not well understood. For example, at p. 1008, col. 3 and p. 1009, cols. 1 and 2, four possible explanations for the non-specific antisense effects of a particular phosphorothioate antisense oligonucleotide are described. Additionally Perez et al. (PNAS v. 21, p.5597-5561, 1994) teaches that one should use caution when considering oligonucleotides with phosphorothioate backbones because of the danger of nuclear transcription factor induction.

Phosphate backbone modifications were known to have unpredictable effects on nucleic acids. Among the complications introduced by phosphorothioate modification is the creation of stereochemistry. The sulfur in a phosphorothioate modification introduces stereochemistry at each bond where it is present, creating distinct versions of the molecule. The two stereochemical forms of the phosphorothioate linkage each produce molecules with biological activities that can be distinct from each other, and distinct from an unmodified nucleic acid, having the same base pairs. Because stereochemistry is introduced at each site with a phosphorothioate bond, a molecule with several or many such bonds is actually an enormously complex mixture of different chemical entities with unpredictable properties. This stereochemistry of phosphorothioates was known prior to 1994. One of skill in the art would not have known whether the introduction of stereochemistry would affect immunostimulation. This stereochemistry does not occur with the usual oxygen. In addition to the stereochemistry, the sulfur atom can have further effects on the activity of the nucleic acid simply due to its being much larger than the oxygen.

Thus, in view of the different teachings between Kuramoto et al/Kataoka et al and Hutcherson et al and the expected different mechanisms of action as well as the unpredictability of phosphorothioate bonds the skilled artisan would not have combined the teachings in the absence of hindsight.

Examiner's Response to Applicant's Arguments:

Applicant's arguments have been fully considered but are not deemed to be persuasive. Examiner accepts amendments that have been made to claims (1 and 11). Examiner understands the recent decision by the Supreme Court in *KSR Int'l Co. v. Teleflex, Inc.*, No 04-1350 (U.S. Apr. 30, 2007). In response to applicant's arguments the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). This is why the references are combined under 35 U.S.C. § 103(a). Examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

The claims are drawn to an oligonucleotide, wherein each internucleotide linkage has a phosphate backbone modification, wherein the phosphate backbone modification is a phosphorothioate. Kuramoto et al teach an oligonucleotide containing 5'-AACGTT-3'. Kuramoto et al teach that all oligonucleotide used were synthesized by the standard phosphoramidite method using an automatic DNA synthesizer. As stated in the prior office action, Goodchild et al teaches an oligonucleotide wherein the phosphate backbone modification is a phosphorothioate (see pg. 167 column 1 last paragraph, column 2 last paragraph). Goodchild et al teaches that backbone modifications are utilized to improve the stability of the DNA to enzymatic degradation (see pg. 167 "Synthesis of Modified Oligonucleotides", pg. 175 "The Effect of Modification on

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Nuclease Resistance"). Goodchild et al. teaches that shorter oligonucleotides are taken up more rapidly (see pg. 176 column 1 paragraph 5). Therefore, in regards to Applicant's assertion that Kuramoto et al hypothesize that the strong activity of bacterial DNA may be due to the palindromic sequences contained therein are irrelevant, the limitations as claimed have been met.

It is noted that Applicant has listed several reference in the response to the present office action. In response to, Applicant's assertion that although it was known in the art that phosphorothioate backbone modifications increase stability of an oligonucleotide it was unknown whether phosphorothioate backbones should be used with immunostimulatory oligonucleotides and at the time of the invention it was not clear how a change in backbone would affect the properties of the immunostimulatory oligonucleotides; In response to Applicant's assertion that stereochemistry is introduced at each site with a phosphorothioate bond, a molecule with several or many such bonds is actually an enormously complex mixture of different chemical entities with unpredictable properties and that stereochemistry of phosphorothioates was known prior to 1994. In response to, Applicant's response of those of ordinary skill in the art did not know the mechanisms through which the nucleic acids of Kataoka et al. or Kuramoto et al. achieved immune stimulation and that without knowledge of the mechanisms through which these nucleic acids achieved immune stimulation, it would have been unpredictable to one of ordinary skill in the art whether a phosphate backbone modification would totally destroy the immunostimulatory capability of the Kataoka or Kuramoto nucleic acids.

Agrawal et al US Patent 5,194,428 before the invention was filed teaches phosphorothioate backbone modifications and that phosphorothioate backbones should be used with immunostimulatory oligonucleotides. Agrawal et al teach a method of inhibiting influenza virus replication through the activity of modified oligonucleotides (oligodeoxynucleotides or oligoribonucleotides). Oligonucleotides (modified) which have antiviral activity against influenza virus as a result of their ability to hybridize to a selected region of influenza virus RNA and inhibit its ability to serve as a template for synthesis of encoded products, as well as compositions which include the

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oligonucleotides. Agrawal et al teach compositions having antiviral activity against influenza virus, which include the oligonucleotides of the present invention, and to a method of administering the oligonucleotides or compositions containing modified oligodeoxynucleotides to an individual for the purpose of inhibiting influenza virus replication (see Agrawal et al abstract claims, and in its entirety).

Furthermore, Hutcherson et al teach that phosphorothioate oligonucleotide analogs include at least one modified internucleotide linkage which, in addition to its enhancement of immune stimulation, can confer stability and enhance uptake of oligonucleotide into cells. An O (oxygen) of the phosphate diester group linking nucleotides is modified to S (sulfur). phosphorothioates often have in vivo half-lives over 24 hours and have been shown to be stable in cells, tissues, and drug formulations. Phosphorothioate oligonucleotide analogs are believed to enter cells by receptor-mediated endocytosis, and cellular uptake is often dependent on length and size, specific sequences, protein binding, and pendant modifications. Liposomes and cationic lipids can significantly enhance the uptake and fate of oligonucleotides and analogs (see line 20). Hutcherson et al further teach oligonucleotides containing a phosphodiester backbone were screened for anti-viral activity in an infectious yield assay and that the sequences showing the best activity in this assay were synthesized as phosphorothioate analogs, the phosphorothioate backbone modification greatly enhancing the antiviral activity of the oligonucleotides through stimulation of a local immune response.

Therefore based on the references as discussed above, it was known in the art that phosphorothioate backbones should be used with immunostimulatory oligonucleotides and a change in backbone would affect the properties of the immunostimulatory oligonucleotides.

Applicant's assertion that although the 3 examples of oligonucleotides provided by Hutcherson et al. happen to contain a CpG, those examples are not including the oligonucleotides formulated in a delivery complex. Examiner disagrees, Hutcherson et al teach oligonucleotides as claimed and can be formulated in a delivery complex i.e. (liposomes see line 20) regardless of if the claim is used in the example of the prior art

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or not. Also, it one would have been motivated at the time the invention was made to incorporate an oligonucleotide in a delivery complex according to Hutcherson et al to because Hutcherson et al teaches that cationic lipids can significantly enhance the uptake and fate of oligonucleotides.

As to Applicant's response of Hutcherson et al. does not teach one of skill in the art that a CpG is required or responsible for immunostimulation. Examiner disagrees Hutcherson et al teach oligonucleotides in a method for stimulating a localized immune response. As stated before the claims are drawn to an oligonucleotide therefore it is irrelevant whether or not the CpG is required or responsible for immunostimulation.

Therefore the combined the teachings of the references, Kataoka et al. or Kuramoto et al, Hutcherson et al., Tokunaga et al. Goodchild, and Cheng et al it would have necessarily produced the claimed invention.

As outlined previously, the instant claims are drawn to an oligonucleotide, comprising: 5'-AACGTT-3', 8-40 nucleotides in length, wherein each internucleotide linkage has a phosphate backbone modification, wherein the phosphate backbone is a phosphorothioate.

Kuramoto et al teach an oligonucleotide, comprising: 5'-AACGTT-3', 8-40 nucleotides in length.

Kuramoto et al teach that all oligonucleotide used were synthesized by the standard phosphoramidite method using an automatic DNA synthesizer.

Kuramoto et al does not teach an oligonucleotide wherein internucleotide linkage has a phosphate backbone modification, wherein the phosphate backbone is a phosphorothioate, and having at least one phosphate backbone modification, wherein the oligonucleotide is linked to a nucleic acid delivery complex, wherein the oligonucleotide is covalently linked to the nucleic acid delivery complex, wherein the nucleic acid delivery complex is a cationic lipid, wherein the nucleic acid delivery complex is sterol. Kuramoto et al does not teach a composition of comprising the oligonucleotide and a pharmaceutically acceptable carrier.

Goodchild et al teaches an oligonucleotide wherein the phosphate backbone modification is a phosphorothioate (see pg. 167 column 1 last paragraph, column 2 last

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paragraph). Goodchild et al teaches that backbone modifications are utilized to improve the stability of the DNA to enzymatic degradation (see pg. 167 "Synthesis of Modified Oligonucleotides", pg. 175 "The Effect of Modification on Nuclease Resistance"). Goodchild et al. teaches that shorter oligonucleotides are taken up more rapidly (see pg. 176 column 1 paragraph 5).

Hutcherson et al teach a composition (see column 5 lines 40-67, column 6 lines 31-43, column 7 lines 55-67, column 10 lines 46-57) comprising: an oligonucleotide delivery complex, wherein the oligonucleotide delivery complex contains an immunostimulatory CpG containing oligonucleotide associated (covalently) with a cationic lipid, wherein the CpG includes a phosphate backbone modification is a phosphorothioate (see abstract, column 5 lines 40-59, column 8 lines 31-50). Hutcherson et al teach a composition comprising a pharmaceutically acceptable carrier (see column 7 lines 49-55), wherein the oligonucleotide is synthetic (see column 8 lines 32-41).

Cheng et al teach oligonucleotides having phosphorothioate linkage covalently linked to a sterol.

It would have been prima facie obvious at the time the invention was made to modify the oligonucleotide of Kuramoto et al by modifying the backbone and inclusion of linking the oligonucleotide in a delivery complex according to Hutcherson et al to because Hutcherson et al teaches that cationic lipids can significantly enhance the uptake and fate of oligonucleotides. It would also have been prima facie obvious to modify the backbone of the oligonucleotide of Kataoka et al to include phosphorothioate taught by Goodchild et al because Goodchild et al teaches that the backbone modifications prevent degradation by nucleases and increase or improve uptake (see section B pg. 167). It would have been prima facie obvious at the time the invention was made to modify the oligonucleotide of Kuramoto et al by inclusion of a sterol because both Cheng et al and Kuramoto both teach oligonucleotide in a delivery complex.

As outlined previously, the instant claims are drawn to an oligonucleotide, comprising: 5'-TGACGTT-3', 8-40 nucleotides in length, wherein each internucleotide

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linkage has a phosphate backbone modification, wherein the phosphate backbone is a phosphorothioate.

Katoaka et al teach an oligonucleotide, comprising: 5'-TGACGTC-3' (BCG-A4a), 8-40 nucleotides in length.

Kataoka et al teaches that the oligonucleotide is synthesized by an automated DNA synthesizer and that the backbone is modified by the standard phosphoramidite method as taught by Tokunaga et al. Tokunaga et al teach that the phosphate backbone modification is a phosphoramidite.

Katoaka et al does not teach an oligonucleotide wherein internucleotide linkage has a phosphate backbone modification, wherein the phosphate backbone is a phosphorothioate, and having at least one phosphate backbone modification, wherein the oligonucleotide is linked to a nucleic acid delivery complex, wherein the oligonucleotide is covalently linked to the nucleic acid delivery complex, wherein the nucleic acid delivery complex is a cationic lipid, wherein the nucleic acid delivery complex is sterol. Kuramoto et al does not teach a composition of comprising the oligonucleotide and a pharmaceutically acceptable carrier.

Goodchild et al teaches an oligonucleotide wherein the phosphate backbone modification is a phosphorothioate (see pg. 167 column 1 last paragraph, column 2 last paragraph). Goodchild et al teaches that backbone modifications are utilized to improve the stability of the DNA to enzymatic degradation (see pg. 167 "Synthesis of Modified Oligonucleotides", pg. 175 "The Effect of Modification on Nuclease Resistance"). Goodchild et al. teaches that shorter oligonucleotides are taken up more rapidly (see pg. 176 column 1 paragraph 5). Tokunaga et al. and Goodchild et al both teach backbone modifications.

Hutcherson et al teach a composition (see column 5 lines 40-67, column 6 lines 31-43, column 7 lines 55-67, column 10 lines 46-57) comprising: an oligonucleotide delivery complex, wherein the oligonucleotide delivery complex contains an immunostimulatory CpG containing oligonucleotide associated (covalently) with a cationic lipid, wherein the CpG includes a phosphate backbone modification is a

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phosphorothioate (see abstract, column 5 lines 40-59, column 8 lines 31-50).

Hutcherson et al teach a composition comprising a pharmaceutically acceptable carrier (see column 7 lines 49-55), wherein the oligonucleotide is synthetic (see column 8 lines 32-41).

Cheng et al teach oligonucleotides having phosphorothioate linkage covalently linked to a sterol.

It would have been prima facie obvious at the time the invention was made to modify the oligonucleotide of Katoaka et al by modifying the backbone and inclusion of linking the oligonucleotide in a delivery complex according to Hutcherson et al to because Hutcherson et al teaches that cationic lipids can significantly enhance the uptake and fate of oligonucleotides. It would also have been prima facie obvious to modify the backbone of the oligonucleotide of Katoaka et al to include phosphorothioate taught by Goodchild et al because Goodchild et al teaches that the backbone modifications prevent degradation by nucleases and increase or improve uptake (see section B pg. 167). It would have been prima facie obvious at the time the invention was made to modify the oligonucleotide of Katoaka et al by inclusion of a sterol because both Cheng et al teach that oligonucleotide in a delivery complex show selective toxicity toward certain specific cancer cells, including some cancer cells which have multiple drug resistance (MDR) against certain established cancer chemotherapeutic agents.

Status of the Claims

3. No claims are allowed.

Claims 28-29, 31-33 and 36 are rejected.

Claims 30 and 34 are withdrawn from consideration.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nina A. Archie whose telephone number is 571-272-9938. The examiner can normally be reached on Monday-Friday 8:30-5:00p.m..

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If attempts to reach the examiner by telephone are unsuccessful, the examiner supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Robert B Mondesi/

Supervisory Patent Examiner, Art
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Nina A Archie

Examiner

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